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10/576,813	12/04/2006	Thomas Stiefel	251508	9037

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EXAMINER	
GWARTNEY, ELIZABETH A	

ART UNIT	PAPER NUMBER
1781	

NOTIFICATION DATE	DELIVERY MODE
03/16/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/576,813	STIEFEL, THOMAS	
	Examiner	Art Unit	
	ELIZABETH GWARTNEY	1781	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,16,17 and 19-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,16,17 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20110127*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The previous 112 2nd Paragraph rejection has been withdrawn in light of applicant's amendments made 27 January 2011.

2. Claims 1-8, 16-17 and 19-23 are pending.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in Graham **v.** John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claim 1-8, 16 and 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frankel ("Supplementation of Trace Elements in Parenteral Nutrition: Rationale and Recommendations") in view of Giordano et al. (US 6,660,293).

Regarding claims 1 and 4, Frankel discloses a total parenteral nutrition composition supplemented with trace elements including **a minimum provision** of 50 meg/day (i.e. 0.05 mg/day) of selenium and 10 mg/day of zinc (p. 587/ paragraph 4, p. 588/paragraph 6). Further, Frankel discloses that in cases of selenium depletion dose of 724 meg/day and 250 meg have been suggested (p. 587/paragraph 1 and 5). Frankel discloses that the parental administration of iron is problematic and does not indicate supplementation of iron in total parenteral nutrition compositions (p.583/paragraph 3, p. 589/paragraphs 4-5).

Given Frankel discloses a total parenteral nutrition composition supplemented with selenium in quantities that overlap with those presently claimed, it would have been obvious to one of ordinary skill in the art at the time of invention to have selected the overlapping portion of the ranges disclosed by the reference because overlapping ranges have been held to be a prima facie case of obviousness. In re Malagari, 182 USPQ 549.

While Frankel discloses a total parenteral nutrition composition supplemented with a recommended daily dose of 10mg zinc, the reference does not explicitly disclose a zinc dosage of 30 mg/day to 100 mg/day.

Giordano et al. teach a nutrition supplementation composition comprising zinc in the range of about 20mg to about 30mg (Abstract, C3/L18-38). Giordano et al. disclose that the

composition is used to treat nutritional deficiencies in patients suffering from a disease state that result in increased oxidative stress or elevated homocysteine levels (C3/L9-17).

Given Frankel discloses a recommended daily dose of 10mg zinc in a nutrition composition and Giordano et al. teach zinc doses of about 20 mg to about 30 mg are known to be used in nutritional compositions, it is clear that the prior art teaches that zinc doses ranging from 10 mg to about 30 mg can be used in nutritional compositions. Therefore, since the claimed daily dose of zinc ranging from 30mg to 100mg overlaps that of the prior art, it would have been obvious to one of ordinary skill in the art at the time of the invention to have selected the overlapping portion of the ranges discloses by the references because overlapping ranges have been held to be a prima facie case of obviousness. In re Malagari, 182 USPQ 549.

Regarding claims 2-3 and 5, modified Frankel discloses all of the claim limitations as set forth above. Given Frankel discloses a parenteral composition, it is clear that the composition is inherently an infusion solution that exists as an aqueous solution and is suitable for parenteral administration.

Regarding claim 6, modified Frankel discloses all of the claim limitations as set forth above. Frankel also discloses total parenteral nutrition compositions comprising chromium and copper (p. 583/paragraphs 3-5, p. 584/paragraphs 1-9, p.585/paragraphs 1-4).

Regarding claims 7-8, modified Frankel disclose all of the claim limitations as set forth above. While Frankel disclose a total parenteral nutrition composition containing selenium and zinc, the reference does not explicitly disclose that composition is formulated as a 10 ml infusion solution that exists as an aqueous solution in an ampoule.

It is well known to package parenteral compositions in parenteral containers, including an ampoule, vial or bag. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to have packaged the total parenteral nutrition composition of Frankel in any parenteral container, including an ampoule, and arrived at the current invention.

Further, it would have been obvious to one of ordinary skill in the art to have formulated the total parenteral nutrition composition in any size of dose, including 10-ml, because change in size is not patently distinct over the prior art absent persuasive evidence that the particular configuration of the claimed invention is significant. See In re Rose, 220 F.2d 459, 105 USPQ 237 (CCPA 1955); In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976); In re Dailey, 357 F.2d 669, 149 USPQ 47 (CCPA 1966). MPEP 2144.04[R-1].

Regarding claims 16 and 19, Frankel discloses administering a total parenteral nutrition composition supplemented with a **minimum provision** of 50 meg/day (i.e. 0.05 mg/day) of selenium and 10 mg/day of zinc to a human (p. 587/ paragraph 4, p. 588/paragraph 6). Further, Frankel discloses that in cases of selenium depletion dose of 724 meg/day and 250 meg have been suggested (p. 587/paragraph 1 and 5). Frankel discloses that the parental administration of iron is problematic and does not indicate supplementation of iron in total parenteral nutrition compositions (p.583/paragraph 3, p. 589/paragraphs 4-5).

While Frankel discloses a total parenteral nutrition composition supplemented with a recommended daily dose of 10mg zinc, the reference does not explicitly disclose a zinc dosage of 30 mg/day to 100 mg/day.

Giordano et al. teach a nutrition supplementation composition comprising zinc in the range of about 20mg to about 30mg (Abstract, C3/L18-38). Giordano et al. disclose that the

composition is used to treat nutritional deficiencies in patients suffering from a disease state that result in increased oxidative stress or elevated homocysteine levels (C3/L9-17).

Given Frankel discloses a recommended daily dose of 10mg zinc in a nutrition composition and Giordano et al. teach zinc doses of about 20 mg to about 30 mg are known to be used in nutritional compositions, it is clear that the prior art teaches that zinc doses ranging from 10 mg to about 30 mg can be used in nutritional compositions. Therefore, since the claimed daily dose of zinc ranging from 30mg to 100mg overlaps that of the prior art, it would have been obvious to one of ordinary skill in the art at the time of the invention to have selected the overlapping portion of the ranges discloses by the references because overlapping ranges have been held to be a prima facie case of obviousness. In re Malagari, 182 USPQ 549.

Regarding claim 20, modified Frankel discloses all of the claim limitations as set forth above. Frankel also discloses administering a total parenteral nutrition composition further comprising chromium and/or copper (p. 583/paragraphs 3-5, p. 584/paragraphs 1-9, p.585/paragraphs 1-4).

Regarding claims 21-22, modified Frankel discloses all of the claim limitations as set forth above. Further, Frankel discloses that in some cases selenium supplemented compositions have been administered daily for 3-4 months (p.587/paragraph 5). Frankel also discloses that zinc supplemented compositions have been administered daily for 92 months (p.588/paragraph 6).

Regarding claim 23, modified Frankel discloses all of the claim limitations as set forth above. Given Frankel disclose a nutritional composition used for the supplementation of trace

elements which comprises chromium, copper, manganese, selenium and zinc, it is clear that the electrolytes are in the form of electrolyte concentrates

7. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Frankel ("Supplementation of Trace Elements in Parenteral Nutrition: Rationale and Recommendations") in view of Giordano et al. (US 6,660,293) as applied to claim 16, and further in view of Ballevre et al. (US 2003/0161863).

Regarding claim 17, modified Frankel discloses all of the claim limitations as set forth above. While Frankel disclose administering a total parenteral nutrition composition comprising selenium and zinc to a human, the reference does not explicitly disclose that the human is an intensive care patient or a sepsis patient.

Ballevre et al. teach an enteral nutrition composition comprising about 40 to about 100 µg /dose of selenium and 5 to 10 mg/dose of zinc (Abstract, [0029]-[0030]) that is administered to critically ill patients including those with sepsis ([0005], [0011]). Further, Ballevre et al. discloses an enteral nutrition composition that does not comprise iron (see Example 1-[0048]-[0050]).

Given that Ballevre et al. teach that is was known to administer nutritional compositions comprising selenium and zinc to critically ill patients including those with sepsis, since Ballevre et al. teach a composition substantially similar l to that of Frankel and that presently claimed, it would have been obvious to one of ordinary skill in the art to have administered the total parenteral nutrition composition of Frankel to critically ill patients including those with sepsis.

Response to Arguments

8. Applicant's arguments filed January 27, 2011 have been fully considered but they are not persuasive.

While Frankel discloses compositions comprising a minimum provision of 50 meg/day (i.e. 0.05 mg/day) of selenium and 10 mg/day of zinc, Applicant submits that Frankel does not disclose a composition containing zinc in the concentrations currently claimed. Applicant further submits that Frankel does not disclose the claimed selenium ranges with sufficient specificity to lead one of ordinary skill in the art to choose the claimed selenium concentrations.

Note, Frankel discloses composition with a minimum of 0.05 mg/day selenium which clearly encompasses the claimed range of 1mg to 2mg. Frankel even recommends, in cases of depletion, administering doses up to 0.724 mg/day selenium (P.587/paragraphs 1 and 5).

Applicant maintains that he has demonstrated that the claimed invention involves surprising and unexpected results (see Rule 132 Declaration of D. Thomas Stifel dated December 28, 2009 and August 13, 2010). Applicant finds that they have clearly demonstrated "the compositions comprising high doses of selenium and zinc which are encompassed by the claims (i.e. selenium doses that are ten-fold higher than those discloses in the prior art), are associated with a low risk of chronic inflammation, infections or diseases associated with free-radical production, as compared to low-dose compositions. Applicant explains that he has "demonstrated that compositions comprising selenium and zinc in the claimed concentrations can be used to successfully treat intensive care patients so that their selenium values and zinc values are maintained at normal levels."

In this case, Applicant has not demonstrated that the criticality of the claimed selenium dosage. Specifically, Applicant has not shown that comparison samples in said examples fairly represent the closest prior art. It is well established that the evidence of unobviousness must be commensurate in scope with the claimed subject matter. See In re Kerkhoven, 626 F.2d 846, 851, 205 USPQ 1069, 1072-73 (CCPA 1980) and In re Clemens, 622 F.2d 1029, 1035, 206 USPQ 289, 896 (CCPA 1980). First the drug described in the declaration (i.e. Tracutil®) comprises 20μg selenium. A dose of 20μg selenium, i.e. 0.002 mg, is over 10 times smaller than the minimum dose recommended by Frankel, i.e. 0.05 mg/day. Clearly, the comparison drug described in the declaration (i.e. Tracutil®) **does not** represent the closest prior art.

In addition, while applicant has established that normal levels of selenium were achieved in the blood and serum of patients after administration of a composition comprising more selenium than a composition which did not produce normal levels of selenium, a person of ordinary skill in the art would not find these results unexpected. One of ordinary skill in the art would expect that the greater the dose the faster normal levels of selenium in the blood and serum would be achieved.

Applicant's arguments with respect to zinc concentration have been addressed by the rejection above.

Applicant argues that the claimed concentrations of selenium and zinc are "well beyond the recommendations in the prior art, as well as the levels in selenium supplement compositions commercially available at the time of the filing of the present application." Applicant submits that "the claimed selenium and zinc concentrations exceed the tolerable uptake intake levels (UL) for selenium recommended by the World Health Organization (WHO). Applicant further

asserts that "the claimed selenium and zinc concentrations are in a range in which, prior to the filing of the present application, one of ordinary skill in the art would have assumed that toxic side effects would result."

First, while the Food and Nutrition Board of the Institute of Medicine (IOM) report that the tolerable upper intake level (UL) of selenium is 400μg/day (i.e. 0.4mg/day); Frankel reports intakes as high as 724 meg/day (i.e. 0.724mg/day) selenium with no signs of toxicity. Applicant is also directed to page 311 of the IOM publications which states that the UL is the "highest level of daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals" and that the "UL is not meant to apply to individuals receiving selenium under medical supervision." In cases of depletion, one of ordinary skill in the art would have considered administering selenium at levels higher than the UL until normal plasma levels are achieved. Given, Frankel discloses that "no instance of Se intoxication by intravenous administration have bee reported', that the risk of selenium toxicity is little, and that zinc is relatively nontoxic, one of ordinary skill in the art would not have assumed that toxic side effects would result at the presently claimed selenium and zinc levels.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELIZABETH GWARTNEY whose telephone number is (571)270-3874. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Keith Hendricks can be reached on (571) 272-1401. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/E. G./
Examiner, Art Unit 1781

/Keith D. Hendricks/
Supervisory Patent Examiner, Art Unit 1781